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K1A 0C9

(21) (A1) 2,082,076

(22) 1992/11/04

(43) 1993/05/06

5,036,6/51

(51) INTL.CL.[5] C07D-213/81; C07D-401/00; C07D-405/00; C07D-409/00; C07D-413/00; C07D-417/00; C07F-009/58; A61K-031/44; A61K-031/495; A61K-031/675

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Pyridine-2,4 and -2,5-Dicarboxamides and Their Derivatives, Process for Their Preparation, and Their Use

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(30) (DE) P 41 36 380.9 1991/11/05

(57) 12 Claims

Canada

CCA 3254 (10-92) 41 7530-21-936-3254

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Abstract of the Disclosure:

Pyridine-2,4- and -2,5-dicarboxamides and their derivatives, process for their preparation, and their use

There are described pyridine-2,4- and -2,5-dicarboxamides and their use as pharmaceuticals, in particular as fibrosuppressants and immunosuppressants.

HOECHST AKTIENGESELLSCHAFT HOE 91/F 350 Dr.Fl/bw

Description

Pyridine-2,4- and -2,5-dicarboxamides and their derivatives, process for their preparation, and their use

Compounds which inhibit the enzymes proline hydroxylase and lysine hydroxylase cause a highly selective inhibition of collagen biosynthesis by affecting the collagen-specific hydroxylation reactions. During these reactions, protein-bound proline or lysine is hydroxylated by the enzymes proline hydroxylase and lysine hydroxylase, respectively. If this reaction is prevented by inhibitors, the result is a non-functional, subhydroxylated collagen molecule, of which only a small amount can be released from the cells into the extracelluar space. Moreover, the subhydroxylated collagen cannot be incorporated into the collagen matrix and is subject to very rapid proteolytic degradation. As a consequence of these effects, the total amount of extracellularly deposited collagen decreases.

It is known that inhibition of proline hydroxylase by known inhibitors, such as α,α'-dipyridyl, results in an inhibition of the Cl_q biosynthesis of macrophages (W. Müller et al., FEBS Lett. 90 (1978), 218; Immunbiology 155 (1978), 47). The classical pathway of complement activation is therefore not available. Proline hydroxylase inhibitors therefore also act as immunodepressants, for example in immune complex disorders.

It is known that the enzyme proline hydroxylase is inhibited effectively by pyridine-2,4- and -2,5-dicarboxylic acid (K. Majamaa et al., Eur. J. Biochem. 138 (1984) 239-245). When these compounds are used in cell cultures, however, they only act as inhibitors when present in very high concentrations (Tschank, G. et al., Biochem J. 238 (1987) 625-633).

DE-A-3,432,094 described pyridine-2,4- and -2,5-dicarboxylic acid diesters having 1-6 carbon atoms in the ester alkyl moiety as pharmaceuticals for inhibiting proline hydroxylase and lysine hydroxylase.

However, the shortcoming of these lower-alkylated diesters is that they are too rapidly cleaved in the organism to give the acids, and that they do not reach the site of action in the cell in sufficiently high concentrations, which makes them less suitable for possible administration as pharmaceuticals.

DE-A-3,703,959, DE-A-3,703,962 and DE-A-3,703,963 provide the general description of mixed ester/amides, higher alkylated diesters and diamides of pyridine-2,4- and -2,5-dicarboxylic acid which are efficient inhibitors of collagen biosynthesis in the animal model.

For example, DE-A-3,703,959 describes, inter alia, the synthesis of N,N'-bis(2-methoxyethyl)pyridine-2,4-dicarboxylic diamide and N,N'-bis(3-isopropoxypropyl)-pyridine-2,4-dicarboxylic diamide.

German Patent Applications DE-A-3,826,471 and DE-A-3,828,140 propose an improved process for the preparation of N,N'-bis(2-methoxyethyl)pyridine-2,4-dicarboxylic diamide. German Patent Application DE-A-3,924,093 proposes novel N,N'-bis(alkoxyalkyl)-pyridine-2,4-dicarboxylic diamides.

There was a need to search for other compounds having an improved pharmacological activity with regard to the inhibition of lysine hydroxylase and proline hydroxylase.

Surprisingly, it has now been found that this object is achieved by the following pyridine-2,4- and -2,5-dicarboxylic diamides.

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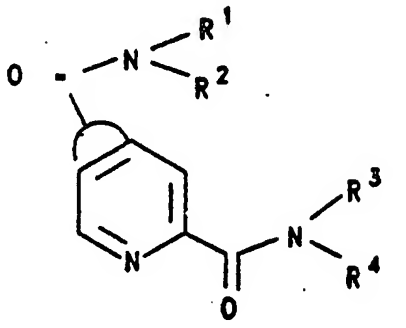
The invention therefore relates to compounds of the formula I



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and are

A a branched or unbranched, aliphatic or cycloaliphatic (C_1-C_{12})-alkyl radical, (C_1-C_{12})-alkenyl radical or a (C_1-C_{12})-alkynyl radical, each of which is monosubstituted or polysubstituted, preferably monosubstituted or disubstituted,

by a (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro,

trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, where the aryl and aralkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, are substituted by 1, 2, 3, 4 or 5 identical or different substituents selected from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, hydroxyl, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, -O-[CH_2-]$_x$$C_f$$H_{(2f+1-g)}$$F_g$, -$OCF_2Cl$, -O-$CF_2$-CHFCl, trifluoromethyl (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or by a substituted (C_6-C_{12})-aryl radical or heteroaryl radical having 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, -O-[CH_2-]$_x$$C_f$$H_{(2f+1-g)}$$F_g$, -$OCF_2Cl$, -$OCF_2$-CHFCl, ($C_1$-$C_8$)-alkylmercapto, ($C_1$-$C_8$)-alkylsulfinyl, ($C_1$-$C_8$)-alkylsulfonyl, ($C_1$-$C_8$)-alkylcarbonyl, ($C_1$-$C_8$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-

alkynylcarbonyloxy, (C_3-C_6)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_6)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, where the aryl and alkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, can be substituted by 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl or (C_1-C_6)-alkoxy,

or by a substituted (C_6-C_{12})-aryloxy radical, (C_7-C_{11})-aralkyloxy radical or heteroaryloxy radical, each of which has 1, 2, 3, 4 or 5 identical or different substituents selected from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, $[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_3)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl,

N,N-di-(C_1-C_4)-alkylsulfamoyl, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl or N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl and which is optionally substituted by up to 3 of the abovementioned identical or different substituents, and one CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or by a radical of the formula II

$$-O-R^5 \qquad (II)$$

in which

R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid, or an alcohol protective group,

B a substituted (C_6-C_{12})aryl radical, (C_7-C_{11})aralkyl radical or heteroaryl radical, each of which is monosubstituted or polysubstituted, preferably mono- or disubstituted,

by hydroxyl, amino (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkylcarbonyloxy, (C_1-C_8)-alkylamino, di-(C_1-C_8)-alkylamino, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, aminoalkyl, N-(C_1-C_8)-alkylamino (C_1-C_{12})-alkyl or N,N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamo-

yloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido,

C a substituted (C_1-C_{12})alkoxy radical, (C_3-C_8)-cycloalkoxy, (C_6-C_{12})-aryloxy radical or a (C_7-C_{11})-aralkyloxy radical, each of which is monosubstituted or polysubstituted, preferably mono- or disubstituted,

by halogen, trifluoromethyl, (C_1-C_6)-alkoxy, hydroxyl, (C_1-C_8)-hydroxyalkyl, NR'R" or cyano

where in each case

R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_7-C_{11})-aralkylcarbonyl or (C_6-C_{12})-arylcarbonyl, or together with the nitrogen, form a saturated heterocyclic ring, preferably a 5- or 6-membered ring,

and the abovementioned radicals R^1, R^2, R^3 and R^4 can occur in combination

with a (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted, preferably mono- or disubstituted, by hydrogen, halogen, hydroxyl, cyano, amino, carboxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkyl- or (C_1-C_4)-dialkylamino or with

a phenyl ring which is mono-, di- or trisubstituted by the radicals halogen, nitro, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, or in combination

with an aryl or heteroaryl radical, each of which can, in turn, optionally be mono-, di- or trisubstituted by halogen, nitro, cyano, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, including all derivatives which have a suitable protective group in their amino or hydroxyl groups,
and the physiologically active salts, and

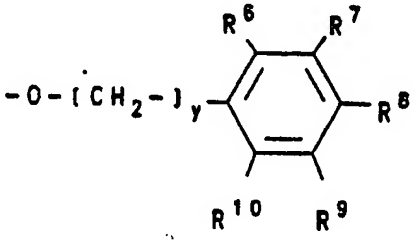
n is 0 or 1,

f is 1 to 8, preferably 1 to 5,

g is 0, 1 to (2f+1), and

x is 0, 1, 2 or 3, preferably 0 or 1.

Aryl, aryloxy, heteroaryl or heteroaryloxy compounds are understood as meaning, in particular, phenyl and naphthyl rings, or unsubstituted 5- and 6-membered heteroaromatic rings having 1, 2 or 3 nitrogen and/or oxygen and/or sulfur atoms, such as pyridyl, pyridazyl, pyrimidyl, pyrazyl, imidazolyl, triazolyl, thienyl, oxazolyl and thiazolyl derivatives, and their benzo-fused derivatives. The radical (C_7-C_{11})-aralkyloxy is preferably understood as meaning a substituted phenylalkyloxy radical of the formula III



(III)

in which

R^6, R^7, R^8 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -O-[CH_2-]$_x$$C_z$$H_{(2z+1-s)}$$F_s$, -$OCF_2Cl$, -O-$CF_2$-CHFCl, ($C_1$-$C_6$)-alkylmercapto, ($C_1$-$C_6$)-alkylsulfinyl, ($C_1$-$C_6$)-alkylsulfonyl, ($C_1$-$C_6$)-alkylcarbonyl, ($C_1$-$C_6$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or two adjacent substituents together are a chain -[CH_2-]$_n$ or -CH=CH-CH=CH-, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR', Y is 1, 2, 3 or 4, preferably 0 and 1, and the remaining of the substituents R^6, R^7, R^8, R^9 and R^{10} are as defined above.

Amino acids which are preferred from amongst those mentioned above are, in particular, the natural α-amino acids.

Amino protective groups are understood as meaning, in particular, such groups as are described in R. Geiger and W. König "The Peptides" Volume 3, "Protection of Functional Groups in Peptide Synthesis", E.G. Gross, J. Meienhofer Edit, Academic Press, New York (1981), in particular pages 7-46.

Such groups are also described in A. Hubbuch, Schutzgruppen in der Peptidsynthese [Protective Groups in Peptide Synthesis], Kontakte 3/79, pages 14-23.

Particularly preferred amino protective groups are the following:

Acetamidomethyl,
1-Adamantyloxycarbonyl,
1-(1-Adamantyl)-1-methyl-ethoxycarbonyl,

Allyloxycarbonyl,
tert-Butyloxycarbonyl,
1-(4-Biphenylyl)-1-methylethoxycarbonyl,
Dicyclohexylcarbodiimide,
α,α-Dimethyl-3,5-dimethoxybenzyloxycarbonyl,
4-Dihydroxyborylbenzyloxycarbonyl,
9-Fluorenylmethyloxycarbonyl,
1-Hydroxybenzotriazole,
3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine,
Isobornyloxycarbonyl,
1-Methyl-cyclobutyloxycarbonyl,
4-Methoxybenzyloxycarbonyl,
Methylsulfonylethyloxycarbonyl,
4-Pyridylmethyloxycarbonyl,
2,2,2-Trichloro-tert-butyloxycarbonyl,
Benzyloxycarbonyl,
halogen-substituted benzyloxycarbonyl,
4-Nitro-benzyloxycarbonyl,
2-Phosphonoethyloxycarbonyl,
Phenylsulfonylethoxycarbonyl,
Toluenesulfonylethoxycarbonyl,
2,3,5-Trimethyl-4-methoxy-phenylsulfonyl,
Benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.

Preferred compounds from amongst those of the formula I whose amino groups are protected are those whose protected amino group is part of this amino acid R^5.

Suitable alcohol protective groups are, in particular, substituted or unsubstituted methyl ethers, ethyl ethers, benzyl ethers, silyl ethers, esters, carbonates or sulfonates.

They embrace the following compounds:

As substituted methyl ethers:
Methoxymethyl, methylthiomethyl, t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxybenzyloxymethyl, (4-methoxyphenoxy)-methyl, guaiacolmethyl, t-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl-S,S-dioxo, 1-[2-chloro-4-methyl)-phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl.

As substituted ethyl ethers:
1-Ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl.

As substituted benzyl ethers:
p-Methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halogenobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl-N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, triphenylmethyl, α-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)-phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4'4"-tris(levulinooxyphenyl)methyl, 4,4'4"-tris-(benzoyloxyphenyl)methyl, 3-(imidazole-1,4'-methyl)bis-(4'4"-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl.

As silyl ethers:
Trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, t-butylmethoxyphenylsilyl.

As esters:
Formates, benzoyl formates, acetates, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, p-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate).

As carbonates:
Methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, p-nitrophenyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, S-benzyl thiocarbonates, 4-ethoxy-1-naphthyl, methyl dithiocarbonates.

Other esters:
2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis-(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (E)-2-methyl-2-butenoate (tigloate), O-(methoxycarbonyl)benzoate, p-P-benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, N-phenylcarbamate, borates, dimethylphosphinothioyl, 2,4-dinitrophenylsulfenate.

As sulfonates:
Sulfates, methanesulfonate (mesylate), benzylsulfonate, tosylates.

The following protective groups are particularly preferred:
(C_1-C_6)-Alkanoyl, (C_1-C_8)-alkylcarbamoyl, di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, (C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{11})-aralkyloxycarbonyl, in particular benzyloxycarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{11})-aralkylcarbonyl, (C_1-C_8)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_8)-alkyl, carbamoyl-(C_1-C_8)-alkyl ester, (C_1-C_{10})-acyloxy-(C_1-C_8)-alkyl, preferably (C_1-C_{10})-alkanoyloxy-(C_1-C_8)-alkyl, benzyloxy-(C_1-C_8)-alkyl, benzyloxycarbonyloxy-(C_1-C_8)-alkyl, (C_1-C_8)-alkoxycarbonyloxy-(C_1-C_8)-alkyl, amino acid esters or tetrahydropyranyl.

Preferred compounds of the formula I are those in which R^1 and/or R^3 are hydrogen or methyl and R^2 and/or R^4 have the abovementioned meanings.

Other preferred compounds of the formula I are those in which R^1 and/or R^3 are hydrogen and R^2 and/or R^4 are

A a branched or unbranched (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted by (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_7-C_{11})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbamoyloxy or N-(C_6-C_{12})-arylcarbamoyloxy, where the aryl and aralkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, are substituted by 1 or 2 identical or different

substituents selected from the series comprising halogen, trifluoromethyl, hydroxyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, $-(C_1-C_3)$-alkoxycarbonyl, carbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy or benzyloxy,

or by a substituted (C_6-C_{12})-aryl radical or heteroaryl radical which has one or two identical or different substituents selected from the series comprising hydroxyl, trifluoromethyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, NR'R", N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy, aminoalkyl or N-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, where R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl or (C_1-C_4)-alkyl,

or by a substituted (C_6-C_{10})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical which has 1 or 2 identical or different substituents selected from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxy, (C_1-C_3)-alkylmercapto, (C_1-C_3)-alkylsulfinyl, (C_1-C_3)-alkylsulfonyl, (C_1-C_3)-alkylcarbonyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy or NR'R" where R' and R" are identical or different and are hydrogen, (C_6-C_{10})-aryl or (C_1-C_4)-alkyl,

or by a radical of the formula II

$$-O-R^5 \qquad (II)$$

in which

R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid,

B is a (C_6-C_{12}) aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl and phenethyl, each of which is monosubstituted by hydroxyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-hydroxyalkyl, amino, (C_1-C_5)-alkylamino, di-(C_1-C_5)-alkylamino, (C_1-C_5)-alkanoylamino, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyloxy, N,N-di-(C_1-C_4)-alkylcarbamoyloxy, or

C is a (C_1-C_8)-alkoxy radical, (C_3-C_8)-cycloalkoxy radical, (C_6-C_{12})-aryloxy radical and (C_7-C_{11})-aralkyloxy radical,

n is 0 or 1,

f is 1 to 8, preferably 1 to 5,

g is 0, 1 to (2f + 1),

x is 0, 1, 2 or 3, preferably 0 or 1, and

where the abovementioned radicals R^1, R^2, R^3 and R^4 can occur in combination

with a (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted, preferably mono- or disubstituted, by hydrogen, halogen, hydroxyl, amino, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkyl- or (C_1-C_4)-dialkylamino or a phenyl ring which is mono-, di- or trisubstituted by the radicals halogen, nitro, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and also in combination with an aryl or heteroaryl radical which, in turn, can optionally be monosubstituted or disubstituted by halogen, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, including all derivatives which have a protective group in the respective amino or hydroxyl group, and the physiologically active salts.

Particularly preferred compounds of the formula I are those in which R^1 and/or R^3 are hydrogen and R^2 and/or R^4 are

A an unbranched (C_1-C_{12})-alkyl radical which is monosubstituted

by (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbonyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, (C_1-C_5)-alkanoylamino, (C_3-C_6)-cycloalkanoylamino, (C_6-C_{12})-aroylamino or (C_7-C_{11})-aralkanoylamino, where alkyl, aryl, aryloxy, aralkyl or aralkyloxy, in turn, are substituted by hydroxyl or halogen, in particular fluorine, (C_1-C_3)-alkyl or (C_1-C_3)-alkoxy,

or by a phenyl radical which is monosubstituted by a hydroxyl group, or a substituted phenoxy or benzyloxy radical which is substituted by hydroxyl, halogen or (C_1-C_4)-alkoxy,

or by a radical of the formula II

$$-O-R^5 \qquad (II)$$

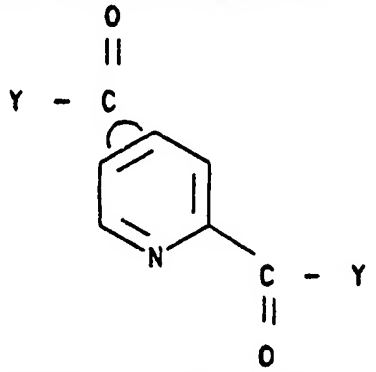
in which R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid which is substituted on the amino group,

B a (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl and phenethyl, which is monosubstituted by hydroxyl, and

C methoxy.

The invention furthermore relates to a process for the preparation of compounds of the formula I which comprises reacting

a compound of the formula IV



(IV)

with a compound of the formulae V

(V)

where R^1, R^2 or R^3, R^4 are as defined in formula I and Y is halogen or hydroxyl or together with the carbonyl group forms an active ester or a mixed anhydride, and, if appropriate, converting the reaction products into their physiologically acceptable salts.

The preparation of compounds of the formula I and the preparation of the starting materials required therefor, unless they are commercially available, will be described hereinafter in greater detail.

The simplest way of preparing the compounds according to the invention is to combine the two components, the pyridine derivative of the formula (IV) and the amine of

the formula (V), in equimolar amounts or in up to approximately 5-fold excess of V, and to react them at temperatures of between -30 and 150°C, preferably at 20 to 100°C, until the reaction is complete. The end of the reaction can be determined by means of thin-layer chromatography (DC check). In a variant of this process, the reaction is carried out in a suitable solvent such as diethyl ether or dimethoxyethane or tetrahydrofuran, chlorinated hydrocarbons such as methylene chloride, chloroform, tri- or tetrachloroethylene, benzene, toluene or else polar solvents such as dimethylformamide or acetone or dimethyl sulfoxide.

In this process too, an excess of amine of the formula (V), which can be up to approx. 5-fold, can be used. The reaction temperatures are between room temperature and the boiling point of the solvent, temperatures in the range from room temperature to 130°C being particularly preferred.

The reaction can equally be carried out via a mixed anhydride such as ethyl chloroformate, or via an activated ester such as paranitrophenyl ester (Y = $ClCH_2$-COO or NO_2-C_6H_4-O). Suitable methods can be found in Houben-Weyl, Methoden der Organischen Chemie [Methods in Organic Chemistry], Volume XV/2, pages 169 to 183 (mixed anhydride method), or pages 13 et seq. (active ester method), fourth edition, Georg Thieme Verlag, Stuttgart 1974.

If appropriate, the reaction can also be carried out in the presence of bases. Suitable additional bases are inorganic acid scavengers such as carbonates or hydrogencarbonates, for example sodium carbonate, potassium carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, or organic acid scavengers such as tertiary amines, such as triethylamine, tributylamine, ethyl diisopropylamine or heterocyclic amines such as N-alkylmorpholine, pyridine, quinoline or

dialkylanilines.

The compounds of the formula (IV) are preferably reacted with amines of the formula (V) with addition of a water-eliminating agent such as dialkylcarbodiimide, where the alkyl radicals have 1 to 8 carbon atoms which, in the case of the C_3-C_8-compounds, can also be branched or cyclic; dicyclohexylcarbodiimide is preferably employed. A suitable method is described in Houben-Weyl Volume XV/2, pages 103 to 111, Methoden der Organischen Chemie [Methods in Organic Chemistry], 4th Edition, Georg Thieme Verlag, Stuttgart, 1974.

If appropriate, the products can be worked up for example by extraction or by chromatography, for example using silica gel. The isolated product can be recrystallized and, if appropriate, reacted with a suitable acid to give a physiologically acceptable salt. Examples of suitable acids are:

Mineral acids such as hydrochloric and hydrobromic acid as well as sulfuric acid, phosphoric acid, nitric acid or perchloric acid, or organic acids such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, phenylacetic acid, benzoic acid, methanesulfonic acid, toluenesulfonic acid, oxalic acid, 4-aminobenzoic acid, naphthalene-1,5-disulfonic acid or ascorbic acid.

If the starting compounds of the formula (V) are not commercially available, they can be synthesized in a simple manner (for example Organikum, Organisch Chemisches Grundpraktikum [Practical Foundation in Organic Chemistry], 15th Edition, VEB Deutscher Verlag der Wissenschaften, 1976; a survey of the various possibilities can be found in the methodological register, page 822).

For example, the starting compound of the formula (IV) can be obtained by reacting pyridine,-2,4- or -2,5-dicarboxylic acid to give the corresponding pyridine-2,4- or -2,5-dicarboxylic halide, preferably the chloride (by processes known from the literature, for example Organikum, Organisch Chemisches Grundpraktikum [Practical Foundation in Organic Chemistry], 15th Edition, VEB Deutscher Verlag der Wissenschaften, 1976, page 595 et seq.), which is then reacted with a suitable alcohol, for example paranitrobenzyl alcohol, to give the corresponding active ester. Equally, the pyridine-2,4- or -2,5-dicarboxylic acid can also first be converted into a mixed anhydride by addition of a suitable carboxylic acid or carboxylate, such as ethyl chloroformate, and this mixed anhydride is then reacted with the amines (V) to give the products according to the invention. A suitable method is described, for example, in Houben-Weyl, Methoden der Organischen Chemie [Methods in Organic Chemistry], Volume XV/2, pages 169 to 183, 4th Edition, 1974, Georg Thieme Verlag Stuttgart.

The compounds of the formula (I) according to the invention have valuable pharmacological properties and are, in particular, effective as inhibitors of proline hydroxylase and lysine hydroxylase, as a fibrodepressant, immunodepressant and antiatherosclerotic.

The antifibrotic action can be determined with the aid of the carbontetrachloride-induced hepatic fibrosis model. To this end, rats are treated twice weekly with CCl_4 (1 ml/kg) dissolved in olive oil. The test substance is administered daily, if appropriate even twice daily, orally or intraperitoneally, dissolved in a suitable acceptable solvent. The extent of hepatic fibrosis is determined hystologically and the amount of collagen in the liver is analysed by hydroxyproline determination as described by Kivirikko et al. (Anal. Biochem. 19, 249 et seq. (1967)). The fibrogenetic activity can be determined

by radioimmunological determination of collagen fragments and procollagen peptides in the serum. In this model, the compounds according to the invention are active at a concentration of 1-100 mg/kg.

The fibrogenetic activity can be determined by radioimmunological determination of the N-terminal propeptide of the type III collagen or the N- or C-terminal crosslinking domain of the type IV collagen (7s collagen or type IV collagen NC_1) in the serum.

To this end, the concentration of hydroxyproline, procollagen III peptide, 7s collagen and type IV collagen NC in the liver were measured in

a) untreated rats (control),

b) rats who had been administered carbon tetrachloride (CCl_4 control) and

c) rats who had been administered first CCl_4 followed by a compound according to the invention

(this test method is described by Rouiller, C., Experimental toxic injury of the liver; in The Liver, C. Rouiller, Vol. 2, pages 335-476, New York, Academic Press, 1964).

Another model for evaluating the antibiotic action is that of bleomycin-induced pulmonary fibrosis as described by Kelley et al. (J. Lab. Clin. Med. 96, 954, (1980)). The cotton ball granuloma model, as described by Meier et al., Experimentia 6, 469 (1950), can be used for evaluating the action of the compounds according to the invention on the granulation tissue.

The compounds of the formula I can be used as medicaments in the form of pharmaceutical preparations which comprise the compounds of the formula I if appropriate together with acceptable pharmaceutical excipients. The compounds can be used as drugs, for example in the form of pharmaceutical preparations, which comprise these compounds in

the form of a mixture with a pharmaceutical, organic or inorganic excipient which is suitable for enteral, percutaneous or parenteral administration such as, for example, inter alia, water, gum arabic, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols and vaseline.

To this end, they can be administered orally at dosage rates of 0.1-25 mg/kg/day, preferably 1-5 mg/kg/day, or parenterally at dosage rates of 0.01-5 mg/kg/day, preferably 0.01-2.5 mg/kg/day, in particular 0.5-1.0 mg/kg/day. In severe cases, the dosage rates can also be increased. In many cases, however, lower dosage rates suffice. These data are based on an adult person of a body weight of approximately 75 kg.

The invention furthermore comprises the use of the compounds according to the invention in the preparation of pharmaceuticals which can be employed for the treatment and prophylaxis of the metabolic disorders mentioned above.

A further object of the invention are pharmaceuticals comprising one or more compounds of the formula I according to the invention and/or physiologically acceptable salts thereof.

The pharmaceuticals are prepared by processes which are known per se and familiar to a person skilled in the art. As pharmaceuticals, the pharmacologically active compounds (= active substance) according to the invention are employed either as such or, preferably, in combination with suitable pharmaceutical adjuvants or excipients in the form of tablets, coated tablets, capsules, suppositories, emulsions, suspensions or solutions, the active substance content being up to approximately 95%, advantageously between 10 and 75%.

Suitable adjuvants or excipients for the desired pharmaceutical formulation are, besides solvents, gelling agents, bases for suppositories, tableting adjuvants and other active substance excipients, for example also antioxidants, dispersants, emulsifiers, defoamers, flavor improvers, preservatives, solubilizers or colorants.

The invention will be illustrated in greater detail hereinafter with the aid of examples.

Example 1

Bis-N,N'-(3'-benzoyloxypropyl)pyridine-2,4-carboxamide

a) 25 g (128 mmol) of dimethyl pyridine-2,4-dicarboxylate are dissolved in 500 ml of ethanol and refluxed for 4 hours together with 22 ml (282 mmol) of 3-amino-1-propanol.
After the mixture has been allowed to stand overnight at room temperature, the solvent is distilled off in vacuo, and the residue is crystallized from hot ethyl acetate; 28.7 g m.p. 102°-105°C.

b) 0.7 g (2.5 mmol) of the resulting pyridine-2,4-dicarboxylic bis-N,N'-(3-hydroxypropyl)amide are combined with 100 ml of dichloromethane and treated with 0.2 g of 4-N,N-dimethylaminopyridine, 0.8 ml (6 mmol) of triethylamine and dropwise with 0.6 ml (5 mmol) of benzoyl chloride. After 1 hour, the mixture is concentrated and the concentrate is taken up in water. After 1 hour, the mixture is extracted twice by shaking with water and the organic phase is concentrated. The crude product is chromatographed over silica gel using ethyl acetate, yield: 0.95 g of colorless oil.
Empirical formula: $C_{27}H_{27}N_3O_6$ (489)
MS: m/e = 490 ($M + H^+$)

Example 2

Bis-N,N'-[2-(2-methylbenzoyloxy)propyl]pyridine-2,4-dicarboxamide

The title compound is obtained analogously to Example 1 from 0.7 g (2.5 mmol) of pyridine-2,4-dicarboxylic bis-N,N'-(3-hydroxypropyl)amide and 0.66 ml (5 mmol) of 2-methylbenzoyl chloride, yield: 0.90 g of colorless oil.
Empirical formula: $C_{29}H_{31}N_3O_6$ (517)
MS: m/e = 518 ($M + H^+$)

Example 3

2-N-(3-Methoxypropyl)-4-N-[3-(2-methylbenzoyloxy)propyl]-pyridine-2,4-dicarboxamide

10.3 g (40 mmol) of 4-benzyloxycarbonylpyridine-2-carboxylic acid are dissolved in 160 ml of anhydrous tetrahydrofuran and, at 0°C, treated with 6 ml (43 mmol) of triethylamine. After 10 minutes, 4.1 ml (43 mmol) of ethyl chloroformate are added dropwise, and the mixture is stirred for 30 minutes at 0°C.
4.4 ml (43 mmol) of 3-methoxypropylamine are then added, the mixture is stirred for 1 hour at 0°C and concentrated in vacuo at room temperature, the product is taken up in dichloromethane, the mixture is washed with saturated $NaHCO_3$ solution, dried and freed from solvent, and 11.2 g of 4-benzyloxycarbonyl-N-(3-methoxypropyl)pyridine-2-carboxamide are obtained. 6.0 g (18.3 mmol) of this compound are combined with 15 ml of 3-amino-1-propanol and the mixture is stirred for 1 hour at 80°C. The excess reagent is distilled off in vacuo and the residue is crystallized from ethyl acetate, yield: 4.8 g of 2-N-(3-methoxypropyl)-4-N-(3-hydroxypropyl)pyridine-2,4-dicarboxamide, m.p. 71-73°C.

2.0 g of this compound are acylated analogously to Example 1 using 2-methylbenzoyl chloride. After silica gel chromatography using ethyl acetate, 2.4 g of the title compound are obtained as a colorless, oily product.
Empirical formula: $C_{22}H_{27}N_3O_5$ (413.5)
MS: m/e = 414 ($M + H^+$)

Example 4

2-N-(3-Hydroxypropyl)-4-N-[3-(2-methylbenzoyloxy)propyl]-pyridine-2,4-dicarboxamide

1.6 g (3.86 mmol)of the title compound of Example 3 are combined with 50 ml of dichloromethane, and 4.5 ml of 1 M boron tribromide solution in hexane (4.5 mmol)are added dropwise at -25°C. After DC check, a further 1.5 ml of this solution are added dropwise, and, after 0.5 hour, the mixture is heated to room temperature and extracted by shaking with saturated $NaHCO_3$ solution, the organic phase is dried and concentrated, and the oily residue is chromatographed on silica gel using ethyl acetate/-methanol. 0.61 g of the title compound crystallize from ethyl acetate,
m.p. 78-80°C
Empirical formula: $C_{21}H_{25}N_3O_5$ (399.4)
MS: m/e = 400 ($M + H^+$)

Example 5

2-N-(3-Methoxypropyl)-4-N-[3-(N-cyclohexylcarbamoyloxy)-propyl]pyridine-2,4-dicarboxamide

2.0 g (6.8 mmol) of 2-N-(3-methoxypropyl)-4-N-(3-hydroxy-propyl)pyridine-2,4-dicarboxamide (cf. Example 3) are dissolved in 250 ml of dichloromethane, and 1.05 ml (7.5 mmol) of cyclohexyl isocyanate are added at 0°C with stirring. The mixture is subsequently refluxed for 1 hour, the reaction is checked by means of DC, a further

1.1 ml of cyclohexyl isocyanate are added, the mixture is heated for a further hour, allowed to cool and treated with water, the organic phase is dried and concentrated, and the oily residue is chromatographed on silica gel using ethyl acetate.
Suitable fractions are concentrated and crystallized using diethyl ether; yield: 1.1 g of the colorless crystalline title compound, m.p. 95-98°C.

Example 6

2-N-(2-Methoxyethyl)-4-N-(3-benzoyloxyethyl)pyridine-2,4-dicarboxamide

a) 150 g of pyridine-2,4-dicarboxylic acid are combined with 1.8 l of methanol and 53.5 g of sulfuric acid (98%) and heated to boiling for 3 hours. After 1 hour, the pyridine-2,4-dicarboxylic acid is largely dissolved. Only a slight cloudiness remains in the mixture. The mixture is poured into ice-water and the finely-crystalline precipitate is allowed to settle, the supernatant is decanted off, the residue is filtered off with suction, washed with water and then with a very small amount of ice-cold MeOH. Yield 70-75 g of 2-methyloxycarbonylpyridine-4-carboxylic acid, m.p. 246-248°C (decomp.). The filtrate is extracted 3 times using CH_2Cl_2, the organic phases are dried and evaporated, the residue is taken up in ethyl acetate, and the mixture is filtered over silica gel (approx. 1 kg). The filtrate is evaporated in vacuo. Yield 90-95 g of dimethylpyridine-2,4-dicarboxylate, m.p. 61-62°C.

b) 50 g of 2-methyloxycarbonylpyridine-4-carboxylic acid and 150 ml of 2-methoxyethylamine give 32.5 g of 2-N-(2-methoxyethyl)-4-carboxamidopyridine-4-carboxylic acid, m.p. 145.5-146°C (from water).

c) 30 g of the above compound are combined with 10 ml of thionyl chloride in 180 ml of toluene and 1 drop of dimethylformamide, the mixture is heated for 3 hours. When cold, 39 ml of triethylamine are added, followed by anhydrous methanol. Filtration with ethyl acetate through silica gel and recrystallization from methanol/water gives 19.8 g of 4-methyloxycarbonyl-N-(2-methoxyethyl)-pyridine-2-carboxamide, m.p. 68-68.5°C.

d) 5.0 g of the above compound are combined with 10 ml of ethanolamine and the mixture is heated to boiling for 30 minutes. 3.0 g of 2-N-(2-methoxyethyl)-4-N-(2-hydroxyethyl)-pyridine-2,4-dicarboxamide, m.p. 124-125°C, are obtained in the form of colorless crystals.

e) The title compound is obtained, analogously to Example 1 from the above compound by reacting it with benzoyl chloride in the presence of triethylamine and 4-N,N-dimethylaminopyridine, as colorless crystals, m.p. 77-78°C
Empirical formula: $C_{18}H_{21}N_3O_5$ (371)
MS: m/e = 372 ($M + H^+$)

Example 7

2-N-(2-Methoxyethyl)-4-N-(2-benzoyloxypropyl)pyridine-2,4-dicarboxamide

The compound is obtained analogously to Examples 6d) and 6e) as a colorless oil,
Empirical formula: $C_{20}H_{23}N_3O_5$ (385)
MS: m/e = 386 ($M + H^+$)

Example 8

2-N-(2-Methoxyethyl)-4-N-[2-(4-hydroxyphenyl)ethyl]-pyridine-2,4-dicarboxamide

The title compound is obtained from 0.24 g of 4-methyloxycarbonyl-2-N-(2-methoxyethyl)pyridine-2-carboxamide (cf. Example 6c)) by melting it with 2-(4-hydroxyphenyl)-ethylamine (tyramine). Filtration with ethyl acetate through silica gel gives 70 mg of colorless needles; m.p. 181-181.5°C (from ethyl acetate);
Empirical formula: $C_{18}H_{21}N_3O_4$ (343)
MS: m/e = 344 ($M + H^+$)

Example 9

Bis-N,N'-[2-(4-methylbenzoyloxy)-ethyl]pyridine-2,4-dicarboxamide

The title compound is obtained analogously to Example 1b) from bis(N,N'-(2-hydroxyethyl)pyridine-2,4-dicarboxamide and 4-methylbenzoyl chloride as colorless crystal powder, m.p. 165-166°C.
Empirical formula: $C_{27}H_{27}N_3O_6$ (489)
MS: m/e = 490 ($M + H^+$)

Example 10

Bis-N,N'-(2-benzoyloxyethyl)pyridine-2,4-dicarboxamide analogously to Example 1b)
colorless needles, m.p. 139-140°C
Empirical formula: $C_{25}H_{23}N_3O_6$ (461)
MS: m/e = 462 ($M + H^+$)

The meanings in the tables below are as follows:

Ph	phenyl
Me	methyl
Et	ethyl

Pr	propyl
Bu	butyl
Bn	benzyl
Pen	pentyl
Hex	hexyl
THP	tetrahydropyranoyl
n	unbranched chain
c	cyclo
i	iso.

R^1/R^2 and R^3/R^4 means that either R^1 or R^2 and R^3 or R^4, respectively, is the radical mentioned. The substituent which remains in each case is hydrogen.

The compounds are in each case 2,4-disubstituted pyridine derivatives.

Ex.	R^1/R^2	R^3/R^4
11	$CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ O\ CO\ Ph$
12	$CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ O\ CO\ NH\ Et$
13	$CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ O\ CO\ NH$-nBu
14	$CH_2\ CH_2\ O\ CO\ OEt$	$CH_2\ CH_2\ O\ CO\ Ph$
15	$CH_2\ CH_2\ O\ CO\ OEt$	$CH_2\ CH_2\ O\ CO\ NH$ c-Hex
16	$CH_2\ CH_2\ O\ CO\ NH$ n-Bu	$CH_2\ CH_2\ O\ CO\ Ph$
17	$CH_2\ CH_2\ O\ CO\ NH$ n-Bu	$CH_2\ CH_2\ O\ CO\ NH$ n-Bu
18	$CH_2\ CH_2\ O\ CO\ NH\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ O\ CO\ NH$ n-Bu
19	$CH_2\ CH_2\ O\ CO\ NH\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ O\ CO\ NH\ CH_2\ CH_2\ OH$
20	$CH_2\ CH_2\ O$ THP	$CH_2\ CH_2\ O$ THP
21	$CH_2\ CH_2\ O$ THP	$CH_2\ CH_2\ O\ CO\ Ph$
22	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$
23	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH\ Et$
24	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ n-Bu
25	$CH_2\ CH_2\ CH_2\ O\ CO\ O\ Et$	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$
26	$CH_2\ CH_2\ CH_2\ O\ CO\ O\ Et$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ c-Hex
27	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ n-Bu	$CH_2\ CH_2\ CH_2\ O\ CO\ Ph$
28	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ n-Bu	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ n-Bu

Ex.	R^1/R^2	R^3/R^4
29	CH_2 CH_2 CH_2 O CO NH CH_2- CH_2 OH	CH_2 CH_2 CH_2 O CO NH n-Bu
30	CH_2 CH_2 CH_2 O CO NH CH_2- CH_2 OH	CH_2 CH_2 CH_2 O CO NH CH_2 CH_2 OH
31	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 CH_2 O THP
32	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 CH_2 O CO Ph
33	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO c-Hex
34	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO c-Pen
35	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO O Et
36	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO O n-Bu
37	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO O c-Hex
38	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO Ph
39	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO i-Pr
40	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO O Ph
41	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CH_2 CH_2 O Me
42	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CH_2 CH_2 O Et
43	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CH_2 CH_2 O Ph
44	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O Ph
45	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O THP
46	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO NH Et
47	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO NH Pr
48	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO NH n-Bu

Ex.	R^1/R^2	R^3/R^4
49	CH_2 CH_2 O CH_3	CH_2 CH_2 CH_2 O CO NH c-Hex
50	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO c-Hex
51	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO c-Pent
52	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO O Et
53	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO O n-Bu
54	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO O c-Hex
55	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO O Ph
56	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO (2-Me Ph)
57	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO Ph
58	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O- Me
59	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O- Et
60	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O-Ph
61	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O Ph
62	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O THP
63	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Et
64	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Pr
65	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH n-Bu
66	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH c-Hex
67	CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Ph

Ex.	R^1/R^2	R^3/R^4
68	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO$ c-Hex
69	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO$ c-Pen
70	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ O$ Eth
71	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ O$ n-Bu
72	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ O$ c-Hex
73	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO$ Ph
74	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO$ i-Pr
75	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ O$ Ph
76	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CH_2\ CH_2\ O$ Me
77	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CH_2\ CH_2\ O$ Et
78	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CH_2\ CH_2\ O$ Ph
79	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O$ Ph
80	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O$ THP
81	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ Et
82	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ Pr
83	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ n-Bu
84	$CH_2\ CH_2\ CH_2\ O\ CH_3$	$CH_2\ CH_2\ CH_2\ O\ CO\ NH$ c-Hex
85	$CH_2\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ CH_2\ O\ CO$ c-Hex
86	$CH_2\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ CH_2\ O\ CO$ c-Pen
87	$CH_2\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ CH_2\ O\ CO$ c-Et
88	$CH_2\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ CH_2\ O\ CO\ C$ n-Bu
89	$CH_2\ CH_2\ CH_2\ OH$	$CH_2\ CH_2\ CH_2\ O\ CO\ O$ c-Hex

Ex.	R^1/R^2	R^3/R^4
90	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO O Ph
91	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO (2-Me Ph)
92	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO Ph
93	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O- Me
94	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O- Et
95	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O- Ph
96	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O Ph
97	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O THP
98	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Et
99	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Pr
100	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH n-Bu
101	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH c-Hex
102	CH_2 CH_2 CH_2 OH	CH_2 CH_2 CH_2 O CO NH Ph
103	CH_2 CH_2 CH_2 O CO c-Hex	CH_2 CH_2 O Me
104	CH_2 CH_2 CH_2 O CO c-Pen	CH_2 CH_2 O Me
105	CH_2 CH_2 CH_2 O CO O Et	CH_2 CH_2 O Me
106	CH_2 CH_2 CH_2 O CO O n-Bu	CH_2 CH_2 O Me
107	CH_2 CH_2 CH_2 O CO O c-Hex	CH_2 CH_2 O Me
108	CH_2 CH_2 CH_2 O CO O Ph	CH_2 CH_2 O Me

Ex.	R^1/R^2	R^3/R^4
109	CH_2 CH_2 CH_2 O CO 2-Me Ph	CH_2 CH_2 O Me
110	CH_2 CH_2 CH_2 O CO Ph	CH_2 CH_2 O Me
111	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O-Me	CH_2 CH_2 O Me
112	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 O Me
113	CH_2 CH_2 CH_2 O CO NH Et	CH_2 CH_2 O Me
114	CH_2 CH_2 CH_2 O CO NH Pr	CH_2 CH_2 O Me
115	CH_2 CH_2 CH_2 O CO NH n-Bu	CH_2 CH_2 O Me
116	CH_2 CH_2 CH_2 O CO NH c-Hex	CH_2 CH_2 O Me
117	CH_2 CH_2 CH_2 O CO NH Ph	CH_2 CH_2 O Me
118	CH_2 CH_2 CH_2 O CO c-Hex	CH_2 CH_2 CH_2 O Me
119	CH_2 CH_2 CH_2 O CO c-Pen	CH_2 CH_2 CH_2 O Me
120	CH_2 CH_2 CH_2 O CO O Et	CH_2 CH_2 CH_2 O Me
121	CH_2 CH_2 CH_2 O CO O n-Bu	CH_2 CH_2 CH_2 O Me
122	CH_2 CH_2 CH_2 O CO O c-Hex	CH_2 CH_2 CH_2 O Me
123	CH_2 CH_2 CH_2 O CO O Ph	CH_2 CH_2 CH_2 O Me
124	CH_2 CH_2 CH_2 O CO 2-Me Ph	CH_2 CH_2 CH_2 O Me
125	CH_2 CH_2 CH_2 O CO Ph	CH_2 CH_2 CH_2 O Me
126	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O Me	CH_2 CH_2 CH_2 O Me
127	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 CH_2 O Me
128	CH_2 CH_2 CH_2 O CO NH Et	CH_2 CH_2 CH_2 O Me

Ex.	R^1/R^2	R^3/R^4
129	CH_2 CH_2 CH_2 O CO NH Pr	CH_2 CH_2 CH_2 O Me
130	CH_2 CH_2 CH_2 O CO NH n-Bu	CH_2 CH_2 CH_2 O Me
131	CH_2 CH_2 CH_2 O CO NH c-Hex	CH_2 CH_2 CH_2 O Me
132	CH_2 CH_2 CH_2 = CO NH Ph	CH_2 CH_2 CH_2 O Me
133	CH_2 CH_2 CH_2 O CO c-Hex	CH_2 CH_2 CH_2 OH
134	CH_2 CH_2 CH_2 O CO c-Pen	CH_2 CH_2 CH_2 OH
135	CH_2 CH_2 CH_2 O CO O Et	CH_2 CH_2 CH_2 OH
136	CH_2 CH_2 CH_2 O CO O n-Bu	CH_2 CH_2 CH_2 OH
137	CH_2 CH_2 CH_2 O CO O c-Hex	CH_2 CH_2 CH_2 OH
138	CH_2 CH_2 CH_2 O CO O Ph	CH_2 CH_2 CH_2 OH
139	CH_2 CH_2 CH_2 O CO 2-Me Ph	CH_2 CH_2 CH_2 OH
140	CH_2 CH_2 CH_2 O CO Ph	CH_2 CH_2 CH_2 OH
141	CH_2 CH_2 CH_2 O Ch_2 CH_2 CH_2 O-Me	CH_2 CH_2 CH_2 OH
142	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 CH_2 OH
143	CH_2 CH_2 CH_2 O CO NH Et	CH_2 CH_2 CH_2 OH
144	CH_2 CH_2 CH_2 O CO NH Pr	CH_2 CH_2 CH_2 OH
145	CH_2 CH_2 CH_2 O CO NH n-Bu	CH_2 CH_2 CH_2 OH
146	CH_2 CH_2 CH_2 O'CO NH c-Hex	CH_2 CH_2 CH_2 OH
147	CH_2 CH_2 CH_2 O CO NH Ph	CH_2 CH_2 CH_2 OH
148	CH_2 CH_2 CH_2 O CO c-Hex	CH_2 CH_2 OH
149	CH_2 CH_2 CH_2 O CO c-Pen	CH_2 CH_2 OH

Ex.	R^1/R^2	R^3/R^4
150	CH_2 CH_2 CH_2 O CO O Et	CH_2 CH_2 OH
151	CH_2 CH_2 CH_2 O CO O n-Bu	CH_2 CH_2 OH
152	CH_2 CH_2 CH_2 O CO O c-Hex	CH_2 CH_2 OH
153	CH_2 CH_2 CH_2 O CO O Ph	CH_2 CH_2 OH
154	CH_2 CH_2 CH_2 O CO 2-Me Ph	CH_2 CH_2 OH
155	CH_2 CH_2 CH_2 O CO Ph	CH_2 CH_2 OH
156	CH_2 CH_2 CH_2 O CH_2 CH_2 CH_2 O-Me	CH_2 CH_2 OH
157	CH_2 CH_2 CH_2 O THP	CH_2 CH_2 OH
158	CH_2 CH_2 CH_2 O CO NH Et	CH_2 CH_2 OH
159	CH_2 CH_2 CH_2 O CO NH Pr	CH_2 CH_2 OH
160	CH_2 CH_2 CH_2 O CO NH n-Bu	CH_2 CH_2 OH
161	CH_2 CH_2 CH_2 O CO NH c-Hex	CH_2 CH_2 OH
162	CH_2 CH_2 CH_2 O CO NH Ph	CH_2 CH_2 OH

Example 163

Bis-N,N'-[2-(4-hydroxyphenyl)-ethyl]pyridine-2,4-dicarboxamide

Analogously to Example 8 from dimethyl pyridine-2,4-dicarboxylate and tyramine

colorless crystals, m.p. 165-166°C

Empirical formula: $C_{23}H_{23}N_3O_4$ (405)

MS: m/e = 40 ($M + H^+$)

Example 164

Bis(N-Methoxy-N-methyl)pyridine-2,4-dicarboxamide

5.1 g (40 mmol) of N-ethylmorpholene are added at 20°C with stirring to 1.67 g (10 mmol) of 2,4-pyridinedicarboxylic acid, suspended in 100 ml of dichloromethane, 2.9 ml (20 mmol) of isobutyl chloroformate are subsequently added dropwise at -15°C, and the mixture is stirred for 20 minutes at -10°C. 1.95 [lacuna] (20 mmol) of N,O-dimethylhydroxylamine hydrochloride are then added, the mixture is stirred for 1 hour at -15°C and allowed to come to 20°C overnight, water is added, the mixture is extracted with dichloromethane, and, after purification of the crude product by column chromatography over silica gel (ethyl acetate/methanol = 10/1), 1.6 g of the title compound are obtained as a colorless oil,

Empirical formula: $C_{11}H_{15}N_3O_4$ (253)

MS: m/e = 254 ($M + H^+$)

Example 165

2-N- -Methoxyethyl)-4-N-(ethyloxy(N-tert.butyloxycarbonylglycyl))pyridine-2,4-dicarboxamide

0.8 g (3 mmol) of 2-N-(2-methoxyethyl)-4-N-(2-hydroxyethyl)pyridine-2,4-dicarboxamide (compound of Example 6d) is combined with 25 ml of anhydrous acetonitrile and 525 mg (3 mmol) of N-butyloxycarbonylglycine, 0.4 ml (3 mmol) of N-ethylmorpholine, 0.45 g (3.3 mmol) of N-hydroxybenzotriazole and 0.62 g (3 mmol) of N,N-dicyclohexylcarbodiimide, and the mixture is stirred for 20 hours at 25°C. The resulting N,N-dicyclohexylurea is filtered off with suction, washed with acetonitrile and concentrated, the product is taken up in dichloromethane, the mixture is extracted with saturated aqueous $NaHCO_3$ solution, the extract is shaken with 10% strength aqueous

citric acid, dried and freed from solvent, and the residue is chromatographed over silica gel.
Empirical formula: $C_{19}H_{28}N_4O_7$ (424)
MS: m/e = 425 ($M + H^+$)

Further examples are: (synthesized from the compound 2-N-(2-methoxyethyl)-4-N-(2-hydroxyethyl)pyridine-2,4-carboxamide described in Example 6d), or from analogous compounds, by benzylation)

2-N-(2-Methoxyethyl)-4-N-(2-benzyloxyethyl)pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-(2-benzyloxyethyl)pyridine-2,4-dicarboxamide

2-N-(3-Methoxypropyl)-4-N-(2-benzyloxyethyl)pyridine-2,4-dicarboxamide

2-N-(2-Hydroxypropyl)-4-N-(2-benzyloxyethyl)pyridine-2,4-dicarboxamide

Bis-N,N'-(benzyloxyethyl)pyridine-2,4-dicarboxamide

(N,N'-Benzyloxypropyl)pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-4-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(3-Hydroxypropyl)-4-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-4-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxypropyl)-4-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,4-dicarboxamide

2-N-(2-Benzyloxyethyl)-4-N-(4-hydroxyethyl)pyridine-2,4-dicarboxamide

2-N-(2-Benzyloxyethyl)-4-N-(4-hydroxypropyl)pyridine-2,4-dicarboxamide

2-N-(2-Benzyloxypropyl)-4-N-(3-hydroxypropyl)pyridine-2,4-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)ethyl]-4-N-(2-hydroxyethyl)-pyridine-2,4-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)ethyl]-4-N-(3-hydroxypropyl)-pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-4-N-(2-benzyloxypropyl)pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-(2-benzyloxypropyl)pyridine-2,4-dicarboxamide

2-N-(3-Methoxypropyl)-4-N-(2-benzyloxypropyl)pyridine-2,4-dicarboxamide

2-N-(2-Hydroxypropyl)-4-N-(2-benzyloxypropyl)pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-4-N-[2-(4-fluorobenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-[2-(4-fluorobenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(3-Hydroxypropyl)-4-N-[2-(4-fluorobenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-4-N-[2-(4-methoxybenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxyethyl)-4-N-[2-(4-methoxybenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(2-Hydroxypropyl)-4-N-[2-(4-methoxybenzyloxy)propyl]-pyridine-2,4-dicarboxamide

2-N-(2-Benzyloxypropyl)-4-N-(2-hydroxyethyl)pyridine-2,4-dicarboxamide

2-N-(2-Benzyloxypropyl)-4-N-(3-hydroxypropyl)pyridine-2,4-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)propyl]-4-N-(2-hydroxyethyl)-pyridine-2,4-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)propyl]-4-N-(3-hydroxypropyl)-pyridine-2,4-dicarboxamide

2-N-(2-Methoxyethyl)-5-N-(2-benzyloxyethyl)pyridine-2,5-dicarboxamide

2-N-(2-Hydroxyethyl)-5-N-(2-benzyloxyethyl)pyridine-2,5-dicarboxamide

2-N-(3-Methoxypropyl)-5-N-(2-benzyloxyethyl)pyridine-2,5-dicarboxamide

2-N-(2-Hydroxypropyl)-5-N-(2-benzyloxyethyl)pyridine-2,5-dicarboxamide

Bis-N,N'-(benzyloxyethyl)pyridine-2,5-dicarboxamide

(N,N'-Benzyloxypropyl)pyridine-2,5-dicarboxamide

2-N-(2-Methoxyethyl)-5-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(2-Hydroxyethyl)-5-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(3-Hydroxypropyl)-5-N-[2-(4-fluorobenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(2-Methoxyethyl)-5-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(2-Hydroxyethyl)-5-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(2-Hydroxypropyl)-5-N-[2-(4-methoxybenzyloxy)ethyl]-pyridine-2,5-dicarboxamide

2-N-(2-Benzyloxyethyl)-5-N-[2-(2-hydroxyethyl)pyridine-2,5-dicarboxamide

2-N-(2-Benzyloxyethyl)-5-N-[2-(3-hydroxypropyl)pyridine-2,5-dicarboxamide

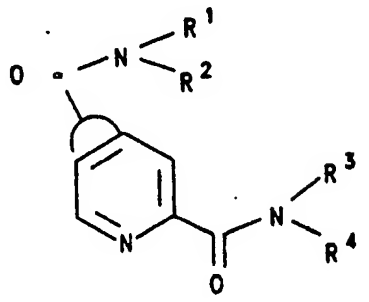
2-N-(2-Benzyloxypropyl)-5-N-[2-(3-hydroxypropyl)pyridine-2,5-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)ethyl]-5-N-(2-hydroxyethyl)-pyridine-2,5-dicarboxamide

2-N-[2-(4-Chlorobenzyloxy)ethyl]-5-N-(3-hydroxypropyl)-pyridine-2,5-dicarboxamide

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound of the formula I



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and are

A a branched or unbranched, aliphatic or cycloaliphatic (C_1-C_{12})-alkyl radical, (C_1-C_{12})-alkenyl radical or a (C_1-C_{12})-alkynyl radical, each of which is monosubstituted or polysubstituted, preferably monosubstituted or disubstituted,

by a (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-

alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, where the aryl and aralkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, are substituted by 1, 2, 3, 4 or 5 identical or different substituents selected from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, hydroxyl, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, trifluoromethyl (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or by a substituted (C_6-C_{12})-aryl radical or heteroaryl radical having 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl,

phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, (C_1-C_8)-alkoxy-carbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxy-carbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkyl-carbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_8-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkyl-sulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkyl-carbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, where the aryl and alkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, can be substituted by 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl or (C_1-C_6)-alkoxy,

or by a substituted (C_6-C_{12})-aryloxy radical, (C_7-C_{11})-aralkyloxy radical or heteroaryloxy radical, each of which has 1, 2, 3, 4 or 5 identical or different substituents selected from the series comprising

hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl or N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl and which is substituted by, in particular, up to 3 of the abovementioned identical or different substituents, and one CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or by a radical of the formula II

$$-O-R^5 \qquad (II)$$

in which

R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid, or an alcohol protective group,

B a substituted (C_6-C_{12})aryl radical, (C_7-C_{11})aralkyl radical or heteroaryl radical, each of which is monosubstituted or polysubstituted, preferably mono- or disubstituted,

by hydroxyl, amino (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkylcarbonyloxy, (C_1-C_8)-alkylamino, di-(C_1-C_8)-alkylamino, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2Cl$, $-OCF_2-CHFCl$, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_8)-

alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, aminoalkyl, N-(C_4-C_8)-alkylamino (C_1-C_{12})-alkyl or N,N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N (C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido,

C a substituted (C_1-C_{12})alkoxy radical, (C_3-C_8)-cycloalkoxy, (C_6-C_{12})-aryloxy radical or a (C_7-C_{11})-aralkyloxy radical, each of which is monosubstituted or polysubstituted, preferably mono- or disubstituted,

by halogen, trifluoromethyl, (C_1-C_8)-alkoxy, hydroxyl, (C_1-C_8)-hydroxyalkyl, NR'R" or cyano

where in each case

R′ and R″ are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_7-C_{11})-aralkylcarbonyl or (C_6-C_{12})-arylcarbonyl, or together with the nitrogen, form a saturated heterocyclic ring, preferably a 5- or 6-membered ring,

and the abovementioned radicals R^1, R^2, R^3 and R^4 can occur in combination

with a (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted, preferably mono- or disubstituted, by hydrogen, halogen, hydroxyl, cyano, amino, carboxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkyl- or (C_1-C_4)-dialkylamino or with a phenyl ring which is mono-, di- or trisubstituted by the radicals halogen, nitro, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, or in combination

with an aryl or heteroaryl radical, each of which can, in turn, optionally be mono-, di- or trisubstituted by halogen, nitro, cyano, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, including all derivatives which have a suitable protective group in their amino or hydroxyl groups,

and the physiologically active salts, and

n is 0 or 1,

f is 1 to 8, preferably 1 to 5,

g is 0, 1 to (2f+1), and

x is 0, 1, 2 or 3, preferably 0 or 1.

2. A compound as claimed in claim 1 in which R^1 and/or R^3 are hydrogen or methyl and R^2 and/or R^4 are as defined in claim 1.

3. A compound as claimed in claim 1 or 2, in which R^1 and/or R^3 are/is hydrogen and R^2 and/or R^4 are/is

A a branched or unbranched (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted by (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_7-C_{11})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbamoyloxy or N-(C_6-C_{12})-arylcarbamoyloxy, where the aryl and aralkyl radicals in the above substituents can also have a heterocyclic nature and/or, like alkyl, are substituted by 1 or 2 identical or different substituents selected from the series comprising halogen, trifluoromethyl, hydroxyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, $-(C_1-C_3)$-alkoxycarbonyl, carbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy or benzyloxy,

or by a substituted (C_6-C_{12})-aryl radical or heteroaryl radical which has one or two identical or different substituents selected from the series comprising hydroxyl, trifluoromethyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, NR'R", N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy, aminoalkyl or N-(C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, where R' and R" are identical or different and are hydrogen,

(C_6-C_{12})-aryl or (C_1-C_4)-alkyl,

or by a substituted (C_6-C_{10})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical which has 1 or 2 identical or different substituents selected from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxy, (C_1-C_3)-alkylmercapto, (C_1-C_3)-alkylsulfinyl, (C_1-C_3)-alkylsulfonyl, (C_1-C_3)-alkylcarbonyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy or NR'R" where R' and R" are identical or different and are hydrogen, (C_6-C_{10})-aryl or (C_1-C_4)-alkyl,

or by a radical of the formula II

$$-O-R^5 \qquad (II)$$

in which

R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid,

B is a (C_6-C_{12}) aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl and phenethyl, each of which is monosubstituted by hydroxyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-hydroxyalkyl, amino, (C_1-C_5)-alkylamino, di-(C_1-C_5)-alkylamino, (C_1-C_5)-alkanoylamino, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyloxy, N,N-di-(C_1-C_4)-alkylcarbamoyloxy, or

C is a (C_1-C_6)-alkoxy radical, (C_3-C_6)-cycloalkoxy radical, (C_6-C_{12})-aryloxy radical and (C_7-C_{11})-aralkyloxy radical,

n is 0 or 1,

f is 1 to 8, preferably 1 to 5,

g is 0, 1 to (2f + 1),

x is 0, 1, 2 or 3, preferably 0 or 1, and

where the abovementioned radicals R^1, R^2, R^3 and R^4 can occur in combination

with a (C_1-C_{12})-alkyl radical which is monosubstituted or polysubstituted, preferably mono- or disubstituted, by hydrogen, hydroxyl, amino, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkyl- or (C_1-C_4)-dialkylamino or a phenyl ring which is mono-, di- or trisubstituted by the radicals halogen, nitro, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and also in combination
aryl or heteroaryl radical which, in turn, can optionally be monosubstituted or disubstituted by halogen, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, including all derivatives which have a protective group in the respective amino or hydroxyl group, and the physiologically active salts.

4. A compound as claimed in any of claims 1 to 3, in which R^1 and/or R^3 are/is hydrogen and R^2 and/or R^4 are/is

A an unbranched (C_1-C_{12})-alkyl radical which is monosubstituted

by (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N (C_1-C_8)-dialkylamino, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-

carbamoyl, N-(C_7-C_{11})-aralkylcarbonyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, (C_1-C_5)-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino or (C_7-C_{11})-aralkanoylamino, where alkyl, aryl, aryloxy, aralkyl or aralkyloxy, in turn are substituted by hydroxyl or halogen, in particular fluorine, (C_1-C_3)-alkyl or (C_1-C_3)alkoxy,

or by a phenyl radical which is monosubstituted by a hydroxyl group, or a substituted phenoxy or benzyloxy radical which is substituted by hydroxyl, halogen or (C_1-C_4)-alkoxy,

or by a radical of the formula II

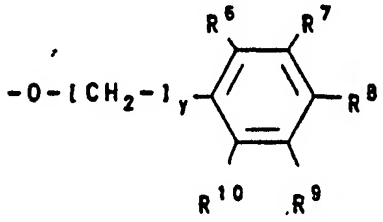
$$-O-R^5 \qquad \text{(II)}$$

in which R^5 is an amino acid bonded via its acyl radical, or a derivative of this amino acid which is substituted on the amino group,

B a (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl and phenethyl, which is monosubstituted by hydroxyl, and

C methoxy.

5. A compound as claimed in any one of claims 1 to 4, wherein a compound of the formula (III)



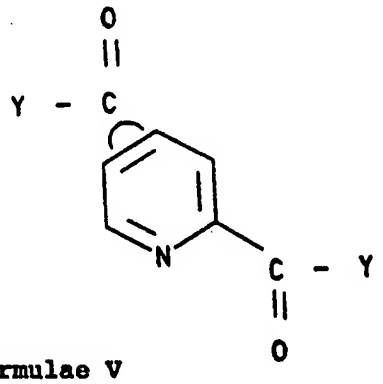
(III)

in which

R^6, R^7, R^8 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or two adjacent substituents together are a chain $-[CH_2-]_n$ or $-CH=CH-CH=CH-$, where one CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR', Y is 1, 2, 3 or 4, preferably 0 and 1, and the remaining of the substituents R^6, R^7, R^8, R^9 and R^{10} are as defined above are employed as the radical (C_7-C_{11})-aralkyloxy.

6. A process for the preparation of a compound as claimed in any of claims 1 to 5, which comprises reacting

a compound of the formula IV



(IV)

and of the formulae V

(V)

where R^1, R^2 or R^3, R^4 have the meanings given in claims 1 to 5, and Y is halogen or hydroxyl or together with the carbonyl group forms an active ester or a mixed anhydride, and, if appropriate, converting the reaction products into their physiologically acceptable salts.

7. A compound as claimed in one of claims 1 to 5 for inhibiting proline hydroxylase and lysine hydroxylase.

8. A compound as claimed in any of claims 1 to 5 for use as fibrodepressants and immunodepressants.

9. A pharmaceutical comprising a compound of the formula I and an acceptable pharmaceutical excipient.

10. The use of a compound of the formula I for influencing the metabolism of collagen and collagen-like substances as well as the biosynthesis of $C1_q$.

11. The use of a compound of the formula I for treating disorders of the metabolism of collagen and collagen-like substances and the biosynthesis of $C1_q$.

12. A process for the preparation of pharmaceuticals for influencing the metabolism of collagen and collagen-like substances as well as the biosynthesis of $C1_q$, wherein the pharmaceutical comprises a compound of the formula I.